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Communication

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Direct C–H α-Arylation of Enones with ArI(O2CR)2 Reagents

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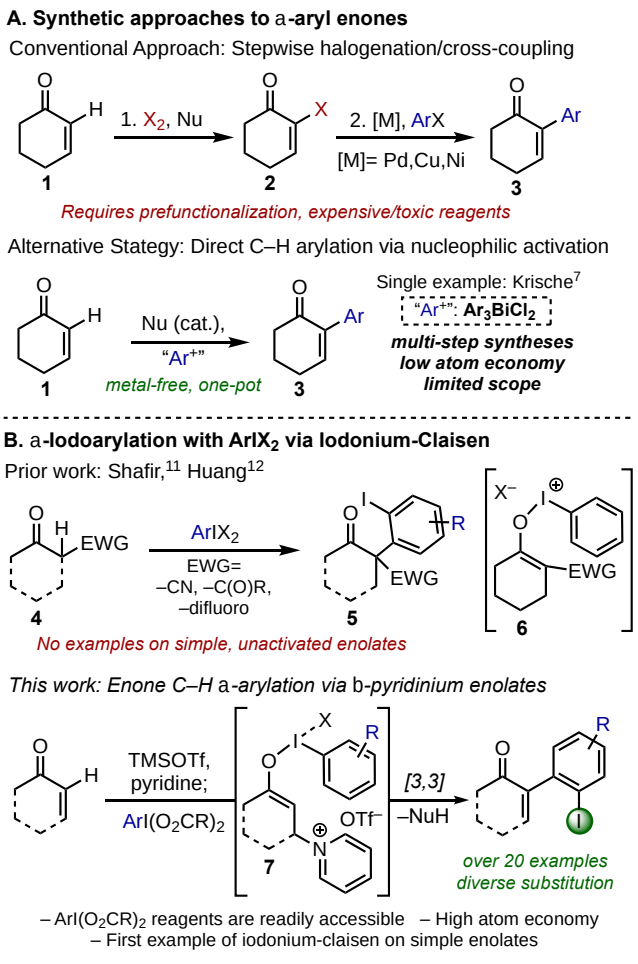
Supporting Information Placeholder

ABSTRACT: The alpha arylation of α,β-unsaturated ketones constitutes a powerful synthetic transformation. It is most commonly achieved via cross coupling of α-haloenones, however this stepwise strategy requires prefunctionalized substrates and expensive catalysts. Direct enone C–H α–arylation would offer an atom and step economical alternative, however such reports are scarce. Herein, we report the metal-free direct C–H arylation of enones mediated by hypervalent iodine reagents. The reaction proceeds via a reductive iodonium Claisen rearrangement of *in situ* β-pyridinium silyl enol ethers. The aryl groups are derived from ArI(O2CCF3)2 reagents, which are readily accessed from the parent iodoarenes. It is tolerant of a wide range of substitution patterns and the incorporated arenes maintain the valuable iodine functional handle. Mechanistic investigations implicate arylation via an umpoled "enolonium" species and that the presence of a β-pyridinium moiety is critical for desired C–C bond formation.

The alpha arylation of carbonyl compounds represents a powerful class of C–C bond forming reaction. While transition metal and organocatalysis have resulted in numerous methods for α-arylation of ketones and aldehydes via enolate and enolate equivalents,[1,2] the corresponding C(sp2)–H arylation of enones (**1**) has seen less development despite the resulting arylated products serving as valuable synthetic intermediates.[3] Enone α-arylation is commonly achieved via first conversion to the α-haloenone (**2**), followed by cross coupling with a suitable arene partner (Scheme 1A), or the roles of the two coupling partners can be reversed.[4] While enabling, such stepwise strategies are not without drawbacks; they require pre-functionalization, sometimes multi-step, of both the starting enone, and often use expensive and/or toxic metals in both the catalysts and cross coupling partners (e.g. Pd, Sn).

Direct enone C–H α-arylation offers a step- and atom-economical alternative, however the development of such methods has proven challenging and no metal-catalyzed approaches have been reported to date.[5,6] In 2000, the Krische laboratory disclosed an elegant solution through the use of nucleophilic phosphine catalysis, in combination with hypervalent bismuth(V) species as aryl transfer reagents (Scheme 1A).[7] Despite affecting metal-free, one-pot enone C–H arylation, this method has not seen broad adoption, likely due to the use of Ar3BiCl2 reagents, which are unfamiliar to most chemists, require multi-step syntheses,[8] and suffer from low atom economy as two of the aryl groups serve as sacrificial "dummy ligands". Taking inspiration from this pioneering report, we became interested in further developing the concept of "nucleophilic activation" as a general platform for direct enone C–H arylation.

Scheme 1. A. Traditional approach to α-arylation and alternative nucleophilic activation strategy B. α-Arylation with I(III) reagents: Prior art and this work

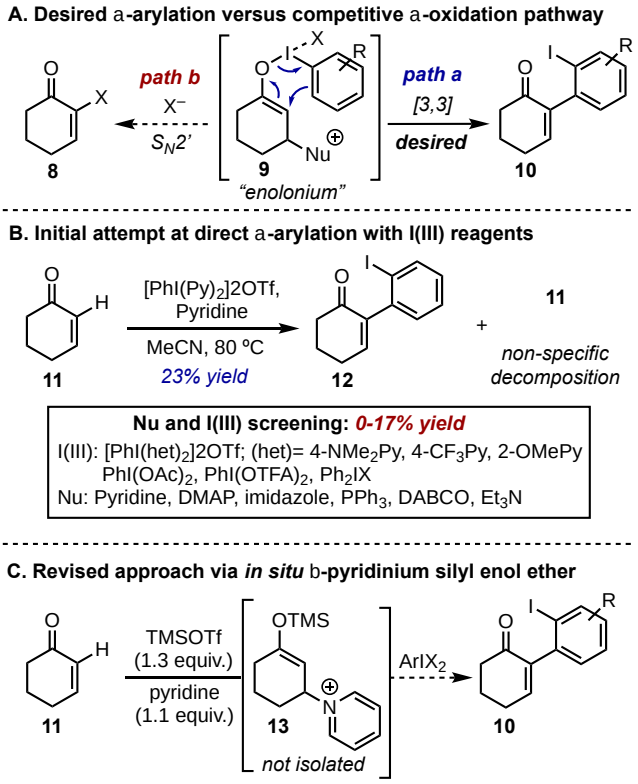


As a part of our laboratory's ongoing interest in hypervalent iodine compounds, we identified I(III)-reagents as a potentially versatile class of arylating reagents to combine with a nucleophilic activation strategy. Hypervalent iodine compounds are attractive due to their low cost, ease of handling, ready accessibility, and versatile reactivity.[9] Within I(III)-species, diaryliodonium salts [Ar_2IX] have seen broad utility as aryl transfer reagents, however they suffer from low atom economy and issues of chemoselectivity with non-symmetrical salts.[10] We were inspired by the recent pioneering work of Shafir[11] and others[12] who have demonstrated that $ArIX_2$ reagents can affect α-(2-iodo)arylation of activated enolates (**4**), including 1,3-dicarbonyls, α-cyanoketones, and α,α-difluorosilyl enol ethers via reductive iodonium Claisen rearrangements of O–I bound enolates (**6**) (Scheme 1B). The use of $ArIX_2$ species as arylating reagents is particularly appealing as they are readily accessible from the parent iodoarenes and notably, the entire aryl iodide motif is transferred intact, making this highly atom economical, and retaining a valuable *ortho*-functional handle for downstream manipulations. However, to date, no successful examples of arylative [3,3] iodonium-Claisen rearrangements on enolates or enol ethers such as those required of the envisioned nucleophilic activation strategy have been described.

Herein, we report the direct C–H α-arylation of enones via reductive iodonium-Claisen rearrangement of *in situ* generated β-pyridinium silyl enol ethers (**7**) and $ArI(O_2CCF_3)_2$ reagents (Scheme 1B). The necessary $ArI(O_2CCF_3)_2$ reagents are readily synthesized from the parent iodoarenes, the reaction shows broad arene scope, and the products retain the *ortho*-iodo functional handle. Mechanistic studies indicate the reaction proceeds via the formation of an O–I enolonium species[13] followed by reductive [3,3]-rearrangement, and that this sequence is highly contingent on the presence of the β-pyridinium moiety. This represents the first example of an iodonium-Claisen rearrangement that circumvents the requirement for α-functionalized enolates (*vide supra*). The synthetic utility of the resulting α-(2-iodo-Ar)enones is demonstrated via the rapid diversification to valuable synthetic building blocks and heterocyclic frameworks.

At the outset of these studies, it was envisioned that the most significant challenge would be controlling for desired arylation over C–X bond formation (Scheme 2A), as the latter is very well-precedented for $ArIX_2$ species and enolates.[9,14] Either product would arise from the same O–I bound "enolonium" intermediate **9**,[13b] which is rendered electrophilic at the α-carbon and is subject to umpolung attack by nucleophiles. Desired α-arylation via a reductive [3,3] rearrangement (path a)[11,12] would need to occur selectively over competitive intermolecular attack by a displaced X-ligand (path b),[9,13a, 13b] which would lead to undesired α-oxidation products (**8**). Based on these two possible mechanisms, we hypothesized that $[ArI(het)_2]X_2$ *or N*-HVIs, which are the subject of ongoing investigations in our laboratory,[15] could be ideally suited for this transformation as the heterocyclic nitrogen ligands are both weakly bound and relatively non-nucleophilic, thus favoring path a.

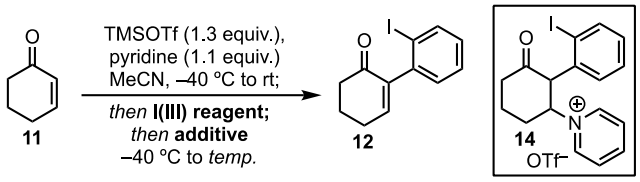
Scheme 2 A. Initial attempts at one-pot arylation B. Modified strategy via β-pyridinium silyl enol ethers



Using cyclohexenone as a model substrate, pyridine-ligated *N*-HVI $[PhI(Py)_2]2OTf$ gave a promising 23% yield of the desired α-iodoarylated enone (**10**) when combined with stoichiometric pyridine as an exogenous nucleophile. Unfortunately, despite screening of *N*-HVIs, other I(III) reagents, β-nucleophiles, and reaction conditions, the yield of arylation could not be improved. We hypothesized that the low yields could be the result of competitive background reactions between the I(III) reagents and the nucleophiles (i.e. ligand exchange, oxidative degradation, ligand coupling). To address this, a sequential, one-pot arylation process was envisioned wherein stoichiometric generation and trapping of an *in situ* enolate would be followed by addition of the $ArIX_2$ species. To this end, it was found that treatment with TMSOTf and pyridine, under slightly modified conditions of those reported by Kim,[16] gave clean conversion to β-pyridinium silyl enol ether **13** as determined by ^{1}H-NMR (Scheme 2C). With efficient conditions for silyl enol ether generation in hand, α-arylation of *in situ* generated **13** was then examined (Table 1), beginning with $[PhI(Py)_2]2OTf$ which gave **12** in a similar 30% yield when the reagent was added at low

temperature and then warmed to 80 °C for 18h (entry 1). Turning to other X-ligands, $PhI(O_2CCF_3)_2$ gave an improved yield of 46% after 12h (entry 2); interestingly, no α-oxidation products were observed and the only other species present by NMR was assigned as intermediate arylated pyridinium salt **14**, which was not stable to isolation. An NMR study then revealed that α-arylation occurred rapidly (<10 min) at low temperature and that final conversion of **14** to **12** was in fact the slow step. Based on this finding, various additives were examined to facilitate elimination of the β-pyridinium moiety. The addition of NEt_3 gave a significant boost in yield to 83% at just 40 °C (entry 3) and the use of acidic silica/MeOH gave further improvement to 90% (entry 4). The use of $PhI(OAc)_2$ was less efficient under both basic and acidic conditions (entries 5 and 6). For comparison, arylation was then attempted with diaryliodonium salts (entries 7 and 8), which have been shown to efficiently arylate silyl enol ethers,[3a, 10, 17] however no reaction was observed, highlighting the unique reactivity of these β-pyridinium species.

Table 1. Optimization of α-arylation of *in situ* β-pyridinium silyl enol ether



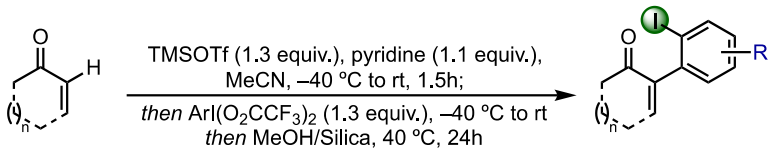
Entry	I(III) reagent	Temp.	Additive	Yield (%)
1	$[PhI(Py)_2]2OTf$	80 °C[a]	none	30%
2	$PhI(OTFA)_2$	80 °C[b]	none	46%
3	$PhI(OTFA)_2$	40 °C[b]	Et_3N	83%
4	$PhI(OTFA)_2$	40 °C[b]	Silica/ MeOH	90%
5	$PhI(OAc)_2$	40 °C[b]	Et_3N	43%
6	$PhI(OAc)_2$	40 °C[b]	Silica/ MeOH	76%
7	Ph_2IBF_4	80 °C	——	0%
8	NPIF	80°C	——	0%

All screening was performed on 0.360 mmol **11** (1.0 equiv), 0.470 mmol I(III) reagent (1.3 equiv.) in 1.8 mL MeCN (0.2M). [a]Reaction heated 18h [b]Reaction heated 12h

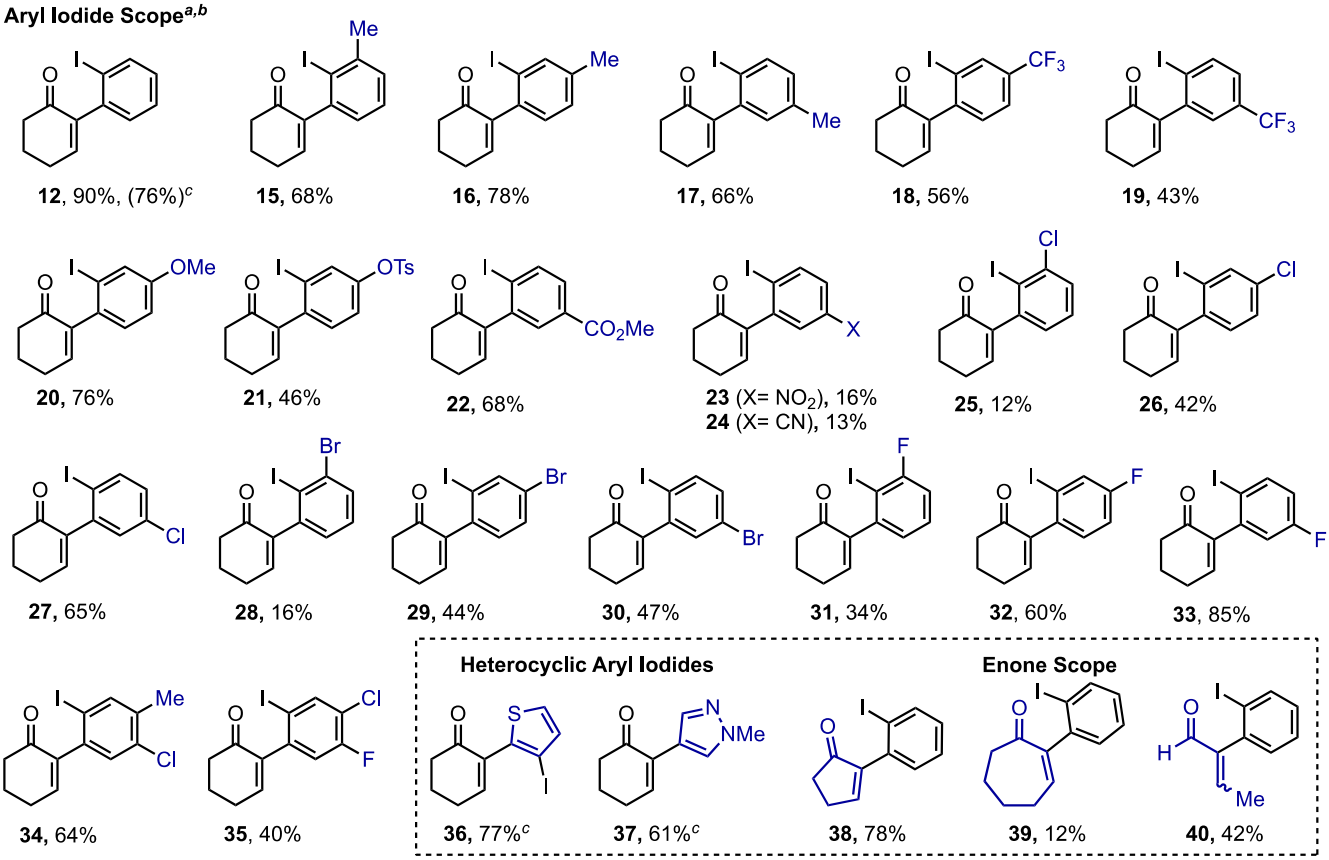
Using this sequential activation strategy, the scope of the arylation was found to be quite general (Table 2). All of the necessary $ArI(O_2CCF_3)_2$ reagents shown can be rapidly synthesized via oxidation of the corresponding commercially available aryl iodides using literature procedures.[18] With regards to the aryl moiety, alkyl groups at the *ortho*-, *meta*-, and *para*-position relative to the iodide were well tolerated giving α-(2-iodoaryl)enones **15**-**19** in good to excellent yields. Electronic-variation including a methoxy (**20**), tosylate (**21**) and ester (**22**) could be incorporated, however more strongly electron-withdrawing groups such as $–NO_2$ (**23**) or –CN (**24**) led to significant drops in yield. The effect of *o*-, *m*-, and *p*- halogen substitution was then examined as these products would provide multiple functional handles and be particularly challenging to synthesize using traditional metal catalyzed cross couplings. While all successfully yielded arylated products (**24**-**32**), a clear trend emerged between yield and substitution pattern (*para*>*meta*>>*ortho*). In the case of **25**, **28**, and **31** the origins of the low yields are hypothesized to arise from dual steric and electronic effects which are detrimental to the initial ligand exchange and arylation steps respectively; together, these lead to a predominance of oxidative degradation byproducts.[19] Next, poly-substituted arenes were found to be amenable to arylation, giving **33** and **34** in good yields. In cases where regioisomeric products were possible, rearrangement occurred with complete regioselectivity for the less hindered site.[20] Electron-rich heteroaromatics could also be incorporated including 3-iodothiophene (**35**) in 77% yield and the desiodo-pyrazole (**36**), the result of a net *ipso*-substitution. With regards to the enone moiety, both cyclopentenone and acyclic crotanaldehyde gave arylated products in good yields (**38**, **40**) whereas arylation of the more conformationally flexible cycloheptenone (**39**) proceeded in only 12%.

The resulting α-(2-iodoaryl)enones can be efficiently converted to synthetic building blocks and polycyclic aromatic heterocycles. Leveraging the carbonyl oxygen, benzofurans in a range of oxidation states could be accessed in excellent yield (**40**-**43**). Turning to nitrogen-containing scaffolds, conversion to the nitro derivative **43** was of interest as this functionality has been utilized in the synthesis of indole natural products and related scaffolds.[3a-3j] Initial screening found that typical nitration procedures led to degradation of the enone moiety,[21] however conversion of **12** to the diaryliodonium salt (see Supporting Information) followed by treatment with KNO_2 gave **43** in good yields.[22]

Table 2. Scope of enone C–H α-arylation with $ArI(O_2CCF_3)_2$ via sequential activation strategy

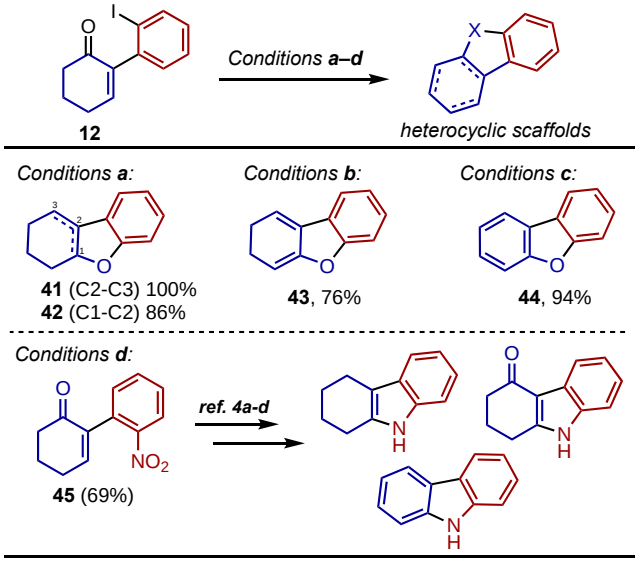


Aryl Iodide Scope[a,b]



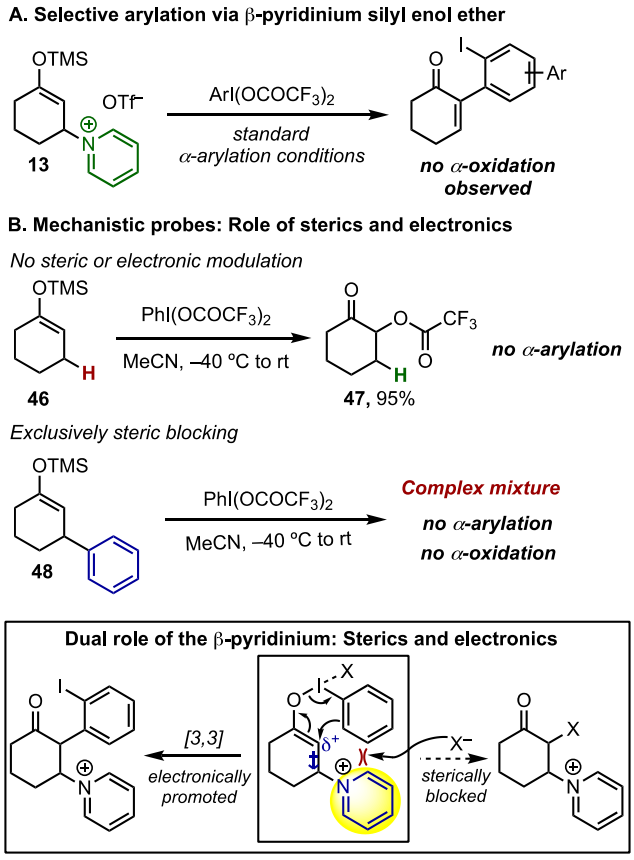
[a]All reactions were performed with 0.36 mmol enone (1.0 equiv) in 1.8 mL MeCN (0.2M). [b]Yields are reported as an average of three trials. [c]Arylation performed with $ArI(OAc)_2$ derivative. In cases of **36** and **37**, analogous $ArI(O_2CCF_3)_2$ reagents were not stable.

Scheme 3. Derivatization of α-(2-iodoaryl)enones



a. to **41:** $NaBH_4$, MeOH; CuI, 1,10-phenanthroline, MePh, 100 °C; then TsOH, 50 °C gives **42**. ***b.*** CuI, 1,10-phenanthroline, mw, 100 °C ***c.*** CuI, 1,10-phenanthroline, mω, 100 °C, then toluene 95 °C ***d.*** *m*-CPBA, anisole, TfOH, CH_2Cl_2; KNO_2, EtOAc, 60 °C

Scheme 4. Mechanistic role of β-pyridinium moiety



Mechanistically, the observed electronic trends favoring the use of electron-rich aromatics (see Supporting Information for analysis of yield vs. σ_{para} values) are consistent with our initial proposal of an "umpoled" enolonium species which undergoes nucleophilic arylation, consistent with previous reports (see Scheme 2A).[11,12,23] A key question surrounded the role of the β-pyridinium moiety in modulating for arylation over C–X bond formation, as α-oxidation side products were not observed under our conditions (Scheme 4A). To begin to probe the origins of this selectivity, β-unsubstituted silyl enol ether **45** was treated with $PhI(OCOCF_3)_2$ and, as expected, this gave exclusively α-oxidized product **47** in near quantitative yield, confirming the predominance of this pathway in the absence of any enolate modulation (Scheme 4B). Next, in order to mimic the sterics of the pyridinium while removing any potential electronic effects, β-phenyl silyl enol ether **46** was subjected to our standard arylation conditions (Scheme 4B). Interestingly, this gave a complex mixture of non-specific degradation products, none of which could be identified as either α-oxidation or α-arylation; this result indicates that sterics alone are not sufficient to achieve efficient α-arylation but do act to inhibit intermolecular pathways. Taken together, these results indicate that the β-pyridinium moiety is likely modulating reactivity via the interplay of both steric and electronic effects (Scheme 4, inset). Steric hinderance is acting to suppress otherwise dominant intermolecular reactions which lead to α-oxidation products, whereas inductive deactivation of the α-carbon further enables the reverse polarity nucleophilic arylation event, likely in an analogous fashion to previously employed α-activating groups.[11,12]

In conclusion, an efficient method for the direct C–H α-arylation of enones with $ArI(O_2CCF_3)_2$ reagents has been developed. The reaction proceeds via *in situ* generation of a β-pyridinium silyl enol ether followed by reductive iodonium-Claisen rearrangement of an "umpoled" enolonium species. This report provides the first example of an iodonium-Claisen arylation that circumvents the previous requirements for α-functionalized enolates. The synthetic utility of the α-(2-iodo-aryl)enones was demonstrated through conversion to various synthetic intermediates and heterocyclic scaffolds. Mechanistically, the β-pyridinium moiety appears critical for promoting the desired arylation over prototypical α-oxidation pathways through both steric and electronic modulation. Further mechanistic investigations, including computational studies, aimed to further understand the steric and electronic effects of the β-pyridinium moiety and aryl iodide moiety on reaction pathway, are the subject of ongoing investigations in our laboratory.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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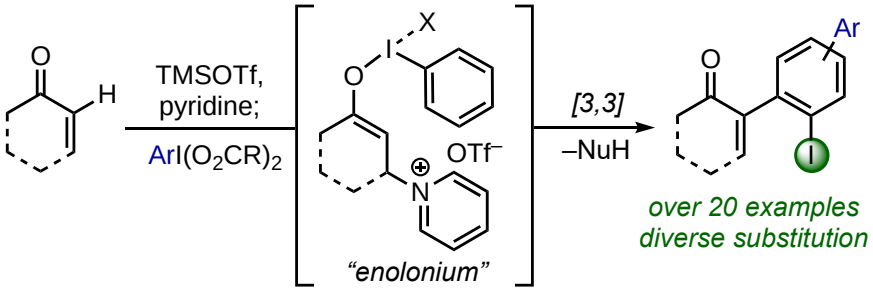

– $ArI(O_2CR)_2$ reagents are readily accessible – Atom economical

– First example of iodonium-claisen on simple enolates